# A Pluripotency and Self-Renewal Program Controls the Expansion of Genetically Unstable Cancer Stem Cells in Pluripotent Stem Cell-Derived Tumors.

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**Public Summary:**

**Scientific Abstract:**
Human germ cell tumors are often metastatic, presumably due to distal site tumor growth by cancer stem cells. To determine whether cancer stem cells can be identified in a transplantation model of testicular germ cell tumor we transplanted murine embryonic germ cells (EGCs) into the testis of adult severe combined immunodeficient (SCID) mice. Transplantation resulted in a locally invasive solid tumor, with a cellular component that generated secondary tumors upon serial transplantation. The secondary tumors were invariably metastatic, a feature not observed in the primary tumors derived from EGCs. In order to characterize the differences between EGCs and the tumor-derived stem cells, we performed karyotype and microarray analysis. Our results show that generation of cancer stem cells is associated with the acquisition of non-clonal genomic rearrangements not found in the originating population. Furthermore, pretreatment of EGCs with a potent inhibitor of selfrenewal, retinoic acid, prevented tumor formation and the emergence of these genetically unstable cancer stem cells. Microarray analysis revealed that EGCs and first and second-generation cancer stem cells were highly similar, however approximately 1,000 differentially-expressed transcripts could be identified corresponding to alterations in oncogenes and genes associated with motility and development. Combined, the data suggest that the activation of oncogenic pathways in a cellular background of genetic instability coupled with an inherent ability to self-renew are involved in the acquisition of metastatic behavior in the cancer stem cell population of tumors derived from pluripotent cells.
_____ ____ Author contributions: A.Conway: Concept and design, Collection and Assembly of data, data analysis and interpretation, manuscript writing; A.L.: Concept and design, Collection and Assembly of data, data analysis and interpretation, manuscript writing; Z.G.: Collection and Assembly of data, data analysis and interpretation; A.P.: Collection of data and data analysis and interpretation; H.W.: Data Analysis and interpretation; J.Z.: Data Analysis and interpretation; M.T.: Data analysis and interpretation, manuscript writing; M.P.: Assembly of Data and Data Analysis; A.Clark: Concept and design, Collection and Assembly of data, data analysis and interpretation, manuscript writing. Anne Conway and Anne Lindgren contributed equally to this work.

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